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Preventive strategies against cytomegalovirus and incidence of α-herpesvirus infections in solid-organ transplant recipients: A nationwide cohort study

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Abbreviations

CMV, cytomegalovirus

HSV, herpes-simplex virus

MMF, mycophenolate mofetil

STCS, Swiss Transplant Cohort Study

VZV, varicella-zoster virus

Abstract

We assessed the impact of antiviral preventive strategies on the incidence of herpes-simplex virus (HSV) and varicella-zoster virus (VZV) infections in a nationwide cohort of transplant recipients. Risk factors for the development of HSV/VZV infection were assessed by Cox PH

regression. We included 2781 patients (56% kidney, 20% liver, 10% lung, 7.3% heart, 6.7% others). Overall, 1264 (45%) patients received antiviral prophylaxis [(val)ganciclovir (n=1126) or (val)acyclovir (n=138)]. Incidences for HSV and VZV infections were 28.9 and 12.1 cases per 1000 person-years, respectively. Incidence of HSV/VZV infections at 1-year post-transplant was 4.6% (95% CI 3.5-5.8) in patients receiving antiviral prophylaxis vs. 12.3% (95% CI 10.7-14) in patients without prophylaxis; this was particularly observed for HSV infections: 3% (95% CI 2.2-4) vs. 9.8% (95% CI 8.4-11.4), respectively. A lower rate of HSV/VZV infections was also seen in donor or recipient CMV-positive patients receiving (val)ganciclovir prophylaxis as compared to a preemptive approach. Female gender (HR 1.663, p=0.001), HSV seropositivity (HR 5.198, p<0.001), previous episodes of rejection (HR 1.95, p=0.004), and use of a preemptive approach (HR 2.841, p=0.017) were significantly associated with a higher risk for HSV infection. While HSV/VZV infections were common after transplantation, antiviral prophylaxis significantly reduced symptomatic HSV infections.

INTRODUCTION

Herpes simplex viruses type 1 and 2 (HSV-1 and -2), and varicella zoster virus (VZV) belong to the *α-herpesvirinae* subfamily and are characterized by establishing latency in the sensitive nerve root ganglia after primary infection (1,2). Both HSV and VZV infections are a common cause of mild to moderate illness in immunocompetent patients. In solid-organ transplant (SOT) recipients, as a consequence of impaired cell-mediated immunity on account of the immunosuppressive drugs, reactivation of HSV and VZV is common, and the clinical manifestation tends to be more severe and prolonged than in immunocompetent individuals (3,4).

The best strategy to prevent HSV and VZV infections after transplantation has not yet been clearly defined. In the absence of anti-herpes prophylaxis, up to 25-35% of seropositive patients will reactivate HSV, particularly in the first weeks following transplantation (5,6). Regarding VZV, the incidence of herpes zoster increases over months after transplantation, and may reach up to 15% of patients at 5 years post-transplant (7,8). Routine antiviral prophylaxis with ganciclovir or valganciclovir for the prevention of cytomegalovirus (CMV) infection has been linked to a lower HSV and VZV reactivation rates (9,10). In patients followed by a preemptive approach (i.e. monitoring of CMV replication and administration of an antiviral drug only in patients with active replication), or at low risk for CMV infection (i.e. recipient CMV seronegative receiving an organ from a CMV seronegative donor [D-/R-]), specific anti-herpes prophylaxis with acyclovir or valacyclovir is generally recommended to reduce the incidence of symptomatic reactivation of these viruses (4,10). However, there are few data analyzing the impact of different anti-CMV preventive strategies using (val)ganciclovir on the incidence of HSV and VZV infection.

Thus, the aim of this nationwide observational cohort study was to describe the clinical characteristics and analyze the risk factors of α-herpesvirus infections after transplantation, with the particular aim of assessing the impact of the different preventive strategies (prophylaxis with (val)ganciclovir vs. preemptive approach) against CMV infection on the incidence of symptomatic HSV and VZV infections.

MATERIAL AND METHODS

Study design

We conducted a nested project based on existing data of a multicentre, nationwide observational Swiss Transplant Cohort Study (STCS) (11). Specifically for the current study, we included all SOT recipients enrolled in the STCS from May 2008 to December 2014. All six Swiss transplant centers participate in the STCS, and for this period approximately 95% of all SOT recipients performed in Switzerland consented to be included. The STCS has been approved by the local Ethics Committee for Clinical Research of all participating centers, and patients gave written informed consent.

Data collection

Clinical data extracted from the STCS database included demographic characteristics, type of transplant, immunosuppressive regimens (induction and maintenance drugs), pre-transplant donor and recipient CMV serostatus as well as the pre-transplant HSV and VZV serologies of the recipient. Data recorded with regards to antiviral prevention were the type of antiviral drug (ganciclovir, valganciclovir, acyclovir, valacyclovir) and the length of prophylaxis duration. Data recorded on symptomatic HSV and VZV infection were the site of infection (mucocutaneous vs. non-mucocutaneous disease), number of episodes per patient, and the use of antiviral therapy for treating active infection. From September 2012, additional data were recorded including reduction of immunosuppression and need for hospitalization following an episode of infection. We also recorded the incidence of acute rejection, graft loss, and mortality.

Clinical definitions

In the STCS, viral infections are classified according to standard definitions created by the Infectious Diseases Study Group of the STCS. Each infection episode was validated by a transplant infectious diseases specialist at each center. Symptomatic HSV or VZV disease was diagnosed when clinical manifestations were compatible with HSV or VZV infection, with or without microbiological confirmation by PCR. Non-mucocutaneous disease was diagnosed in case of clinical manifestations involving the gastro-intestinal tract (i.e: esophagus and stomach), the eye, the respiratory tract, and the central nervous system and/or a positive PCR in a tissue biopsy, corneal scraping or cerebro-spinal fluid, respectively. Patients with a positive PCR in blood were classified as having viremia, irrespective of the presence of other clinical manifestations. Because the extension of the involvement in mucocutaneous infections was not included in the STCS database, we used the need for antiviral therapy, reduction of immunosuppression, and hospitalization as surrogate markers for severity of infection.

Antiviral prophylaxis for CMV was defined as the use of ganciclovir or valganciclovir started within the first 2 weeks post-transplantation. Patients without such a prophylactic treatment who were at risk for CMV disease (D+/R- and R+ patients) were considered as being managed by the preemptive approach, as described previously (12). CMV infection and disease were classified according the definitions published by the American Society of Transplantation guidelines (13). Anti-herpes prophylaxis was defined as the use of acyclovir or valacyclovir in patients not receiving anti-CMV prophylaxis. The use of universal prophylaxis or preemptive approach for CMV and anti-herpes prophylaxis was established according to each center protocol based on CMV serostatus. Because the antiviral prophylaxis (and the type of antiviral drug) depended on the CMV risk constellation, we defined four different groups: 1) CMV D-/R- patients receiving antiviral prophylaxis (either

anti-CMV or anti-herpes), 2) CMV D-/R- patients not receiving anti-CMV or anti-herpes prophylaxis, 3) CMV D+/R- or R+ patients receiving anti-CMV prophylaxis, and 4) CMV D+/R- or R+ patients managed by the preemptive approach. Because only 19 patients of the preemptive approach group received a specific anti-herpes prophylaxis, all D+/R- or R+ patients managed by a preemptive approach were analyzed as a single group irrespectively whether they have received anti-herpes prophylaxis or not. Acute rejection was defined for each organ following the standard international criteria (14).

Statistical analysis

A descriptive analysis was performed to determine the baseline characteristics (age, sex, organ transplanted, type of immunosuppressive therapy, CMV serostatus and HSV/VZV seropositivity), the transplant outcome variables (acute rejection, graft loss, death) and the episodes of HSV/VZV (median of episodes per patient, median time from transplantation, and clinical presentation) of the patients. Cumulative incidences were calculated by organ group to estimate the probability of first HSV or VZV infection events from transplant, treating death before an event as a competing risk, according to the antiviral prophylaxis used. The impact of the antiviral strategy on HSV or VZV reactivation was analyzed as time-dependent risk factor using a Cox proportional hazard regression model adjusting for potential confounding factors such as type of organ, episodes of rejection, age, sex, CMV preventive strategy, CMV infection, and HSV or VZV seropositivity previous to transplant. The impact of the duration of antiviral prophylaxis on the probability of HSV or VZV infection was assessed by logistic regression. All analyses were performed with the statistical software R version 3.2.1. (R Development 2012 Core Team. A language and environment for statistical computing. Available from: http://www.R-project.org 2012).

RESULTS

Study population

A total of 2781 SOT recipients (56% kidney, 20% liver, 10% lung, 7.3% heart, 6.7% others) were included in the study. The median age was 54 years (IQR 42-62) and 64% were male. Seventy-six percent of patients (1643/2155 of patients with available serology) were seropositive for HSV and 95% of the patients (2358/2477) were seropositive for VZV at the time of transplant. Overall, 1264 (45%) patients received antiviral prophylaxis (with either (val)ganciclovir [n=1126] or (val)acyclovir [n=138]) for a mean duration of 144 days (kidney: 117 days, liver: 118 days, lung: 237 days, and heart: 138 days). Baseline characteristics and outcomes of the patients according to the development of HSV, VZV or both HSV/VZV infections are detailed in **Table 1**. The calculated incidences were 28.9 cases per 1000 person-years of follow-up for HSV infection and 12.1 cases per 1000 person-years of follow-up for VZV infection.

Herpes simplex virus infection

The clinical characteristics of HSV infections are described in **Table 2**. Overall, 247 (8.9%) patients developed a total of 289 episodes of symptomatic HSV infection. Eighteen patients developed both HSV and VZV infections. The incidence at 1, 3 and 6 years post-transplant of first HSV infection was 6.7% (95% CI 5.8-7.7), 8.7% (95% CI 7.6-9.8) and 9.9% (95% CI 8.7-11.2), respectively (**Figure 1**), with a median time of onset of 66 days after transplantation (IQR 21-336). The incidence by type of organ at 1 year post-transplantation was 9.4% in heart, 8.4% in liver, 6.5% in kidney, and 1.8% in lung transplant recipients. Overall, 86% of HSV infections were episodes of mucocutaneous disease. Episodes of non-mucocutaneous disease included 16 infections of the gastrointestinal tract (40%), 12 episodes

of keratitis (30%), 6 episodes of respiratory tract infection (15%), and one episode of central nervous system (CNS) infection (2.5%).

Varicella-zoster virus infection

One hundred-ten patients (4.0%) developed VZV infections (including the 18 patients who additionally developed HSV infection), for a total of 121 episodes (**Table 2**). The incidence of VZV infection at 1, 3 and 6 years post-transplant was 2.1% (95% CI 1.6-2.7), 3.5% (95% CI 2.8-4.2) and 4.4% (95% CI 3.5-5.4), respectively (**Figure 1**). The median time of onset was 249 days after transplantation (IQR 65-738). The incidence of VZV infection by transplant type at 1 year post-transplant was 2.3% in kidney, 1.6% in liver, 5.5% in heart, and 0% in lung transplant recipients. Six cases of non-mucocutaneous involvement were diagnosed, including 3 episodes of CNS disease, 2 of keratitis, and 1 case of VZV viremia.

Impact of the antiviral preventive strategy on HSV and VZV infections

We analyzed the incidence of both HSV and VZV infections according to the CMV serostatus and the antiviral preventive strategy used after transplant (**Figure 2**). Overall, the incidences of HSV/VZV infections at 1 year post-transplant were 4.6% (95% CI 3.5-5.8) in patients receiving antiviral prophylaxis [either (val)ganciclovir of (val)acyclovir] vs. 12.3% (95% CI 10.7-14) in patients without any antiviral prophylaxis ($p<0.001$) (**Figure 2A**). The impact of antiviral prophylaxis was more manifest when looking specifically at HSV infection: 3% (95% CI 2.2-4) vs. 9.8% (95% CI 8.4-11.4) in patients with and without prophylaxis, respectively.

According to CMV serostatus, in D+/R- or R+ patients the incidences of HSV/VZV infections were 4.5% (95% CI 3.4-5.9) in patients receiving (val)-ganciclovir prophylaxis and 13.2% (95% CI 11.3-15.3) in patients followed by the preemptive approach ($p<0.001$). In D-

/R- patients, the incidence of HSV/VZV infection at 1 year post-transplantation was 2.5% (95% CI 0.8-5.9) vs. 10.4% (95% CI 7.7-13.7) in patients with and without any antiviral prophylaxis (p=0.01), respectively (**Figure 2B**).

When looking separately according to each viral infection, the incidence of HSV infection was 2.9% (95% CI 2.1-4.1) in CMV D+/R- or R+ patients receiving (val)-ganciclovir prophylaxis vs. 10.6% (95% CI 8.9-12.5) in patients followed by the preemptive approach (p<0.001, prophylaxis vs. preemptive); and 1.2% (95% CI 0.2-4.1) in CMV D-/R- patients receiving antiviral prophylaxis vs. 8.2% (95% CI 5.8-11.1) in D-/R- patients without antiviral prophylaxis (p=0.01, with vs. without prophylaxis) (**Figure 2C**). There were no differences in the incidence of VZV infection according to the antiviral preventive strategy received (p=0.53) (**Figure 2D**).

Risk factors for HSV and VZV infections

Variables significantly associated with a higher risk for HSV infection in the multivariate analysis were female gender, HSV seropositivity, previous episodes of acute rejection, and the use of a preemptive approach for CMV prevention in D+/R- or R+ patients as compared to the reference group of D-/R- with antiviral prophylaxis (**Table 3**). Previous episodes of CMV infection were a significant risk factor for HSV infection in the univariate, but not in the multivariate model.

Because the impact of antiviral prophylaxis on HSV infections seemed to be more important early after transplant, we built a new Cox PH model taking into consideration the period post transplant (i.e. <6 months vs. > 6 months). As compared to the reference group of D-/R- with antiviral prophylaxis, the risk for HSV infection in D+/R- and R+ patients followed by the preemptive approach was only significant during the first 6 months post transplant (HR 6.102 [95% CI 1.469 - 25.353], p=0.013), as compared to > 6 months post

transplant (HR 1.218 [95% CI 0.417 - 3.383], p=0.719). The impact of being seropositive for HSV was also higher during the first 6 months post transplant (HR 7.582 [95% CI 3.072 - 18.716], p<0.001), than later on (HR 3.102 [95% CI 1.313 - 7.329] p=0.01).

For VZV infection, as compared to kidney transplantation, heart transplantation was associated with a higher risk and lung transplantation with a lower risk of VZV infection, although this was not statistically significant. Age, sex, previous episodes of rejection, VZV seropositivity, and the antiviral preventive strategy were not significantly associated as risk/protective factors for VZV infection in this model (**Table 4**).

Of note, no particular induction or maintenance immunosuppressive regimen was associated with a higher risk for the development of HSV or VZV infections.

Impact of the duration of antiviral prophylaxis on the incidence of HSV and VZV infections

We next assessed in a logistic regression the risk of HSV and VZV infections according whether the patients had received no antiviral prophylaxis, less than 3 months, between 3-6 months, or more than 6 months of antiviral prophylaxis (**Table 5**). We found that the longer the duration of prophylaxis, the lower the risk of HSV infection. We did not observe any difference in the incidence of VZV according to the duration of antiviral prophylaxis.

DISCUSSION

Symptomatic HSV and VZV clinical infections were relatively frequent in the Swiss population of SOT recipients, with an incidence during the first year post transplant ranging from 1.8% to 9.4% for HSV and 0% to 5.5% for VZV, according to the type of organ transplant. These numbers are somewhat lower than those reported in other cohorts (7,8,15,16), possibly reflecting a continuous improvement in the prevention and management of post transplant viral infections in the current era of transplant medicine.

We found a lower incidence of mostly HSV infections in patients receiving antiviral prophylaxis as compared to patients followed by the preemptive approach or not receiving specific anti-herpes prophylaxis. There are few data in the literature on the impact of antiviral preventive strategies (mostly aimed at preventing CMV infection) on α-herpesvirus infection. In a recent meta-analysis evaluating the efficacy of CMV preventive strategies in SOT recipients (17), both antiviral prophylaxis and preemptive therapy showed similar efficacy in preventing HSV and VZV infections. However, another study including 363 kidney transplant recipients analyzed the incidence of VZV reactivation according to the type of antiviral prophylaxis used. Patients were categorized into 3 groups: preemptive therapy, universal prophylaxis <3 months, and universal prophylaxis >3 months. In this setting, patients followed by preemptive therapy had a higher incidence of infection compared with the others groups (80 vs. 54.5 vs. 13 cases per 1000 person-years) (18). This is in concordance with our results, where the probability of α-herpesvirus infection was higher in patients without antiviral prophylaxis, in particular in patients followed by preemptive therapy, as compared to patients receiving antiviral drugs. We also observed in our study that patients receiving more than three or six month of prophylaxis had the lowest risk for the development of HSV infection. The impact of antiviral prophylaxis was mainly seen for HSV infection, likely due to the lower number of VZV infections and the fact that VZV infections appeared later on after transplantation, when most antiviral drugs were no longer prescribed as prophylaxis. This could be also explained by the presence of natural polymorphism of VZV thymidine kinase and DNA polymerase found in *in vitro* studies, conferring a lower intrinsic antiviral activity of ganciclovir against VZV as compared to HSV (19, 20).

Overall, our data indicate that specific anti-herpes prophylaxis in patients not receiving anti-CMV drugs may further reduce the incidence of HSV and VZV infections. Of note, the antiviral agents approved for the prevention and treatment of herpesvirus infections

act at the same step of virus replication, inhibiting the viral DNA polymerase. Acyclovir and ganciclovir require phosphorylation to be activated by a thymidine kinase in HSV or VZV and by its homolog UL97 protein kinase in CMV. Because acyclovir and valacyclovir are usually well tolerated and are less expensive than anti-CMV drugs, this strategy might be cost-effective in the setting of organ transplantation. This recommendation can be particularly important in case of HSV seropositivity, female patients, and after therapy of acute rejection, the risk factors for HSV infection identified in our study. We found a surprising lower incidence of HSV and VZV infections in lung transplant recipients as compared to other types of transplant. Although higher rates of infection have been previously reported in lung transplant recipients (8,21–24), our results can be explained by a longer duration of antiviral prophylaxis used in these patients as compared to other organ transplants. Finally, we found that both (val)-acyclovir and (val)-ganciclovir seem equally effective for the prevention of α-herpesvirus infection, an expected result but not extensively reported in the literature.

While the most common clinical presentation of α-herpesvirus infection was mucocutaneous, non-mucocutaneous involvement – feared due to its more complicated course - was detected in 10% involving infections of the gastrointestinal tract and keratitis for HSV. Of note, the data included in the STCS database did not allow us to estimate the severity of the clinical presentation, in particular regarding the rate of disseminated herpes zoster and the subsequent incidence of post herpetic neuralgia. However, we could estimate that these infections were associated with a significant burden of disease, as more than 93% of the patients received antiviral treatment and between 8% and 17% of them required hospitalization.

Current immunosuppressive regimens have been related with a higher incidence and more severe clinical manifestations of α-herpesvirus reactivation in some studies. Mycophenolate mofetil (MMF) was identified as an independent risk factor for VZV

reactivation after liver transplantation (7,21,25). Because the majority of the patients received MMF as part of the immunosuppressive regimen, it was difficult to assess the impact of MMF on the risk of infection in our study. Gourishankar et al. found that the use of induction therapy was a risk factor for VZV reactivation after transplantation (7), but this was not confirmed in the present study. Also, we did not identify the use of mTOR inhibitors, an immunosuppressive drug with antiviral properties, as a protective factor for the development of HSV and VZV infections.

This study has several limitations. First and foremost, data on the severity and complications of the mucocutaneous involvement in VZV and HSV infection were not available in the STCS database, so that we were not able to estimate the true burden of disease in view of a potential recommendation for the use of anti-herpes prophylaxis in all patients not receiving anti-CMV drugs. We were not able either to differentiate between HSV-1 and HSV-2 infections, due to the absence of information on the localization of the mucocutaneous disease and the type of viruses involved. Also, we cannot exclude that some infections were underreported, particularly months or years after transplant, when patients are not exclusively followed at the transplant center. Finally, because very few D+/R- or R+ patients followed by the preemptive approach for CMV received anti-herpes prophylaxis, we were not able to analyze them separately from those who did not receive any antiviral drug. Nevertheless, this is probably the largest cohort of SOT recipients with a long follow-up where the incidence and risk factors of these common viral infections have been assessed, and the results from this study may help to delineate current guidelines for the management of HSV or VZV infection in the transplant population (4,26).

In conclusion, in this large nationwide cohort of SOT recipients, HSV and VZV infections were relatively common, with several cases of non-mucocutaneous involvement. Antiviral prophylaxis with (val)ganciclovir or (val)acyclovir had a significant impact on

reducing the incidence of HSV infection after transplantation. Specific anti-herpes prophylaxis might be recommended in patients not otherwise receiving anti-CMV drugs, especially after intensification of immunosuppression for acute rejection.

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Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the American Journal of Transplantation.

Figure legends

Figure 1. Cumulative incidence of HSV and VZV infections after transplantation. HSV, herpes-simplex virus; VZV, varicella-zoster virus.

Figure 2. Probability of HSV and VZV infections after transplantation according to the CMV serostatus and the antiviral preventive strategy. Probability of HSV or VZV infection in patients with (light blue line) or without (green line) antiviral prophylaxis ($p<0.001$, with vs. without prophylaxis) (A). Probability of infection in CMV D-/R- patients receiving antiviral prophylaxis (yellow line), CMV D+/R- or R+ patients receiving antiviral prophylaxis (grey line), CMV D-/R- patients not receiving antiviral prophylaxis (green line), and CMV D+/R- or R+ followed by the preemptive approach (magenta line): HSV or VZV infection ($p<0.001$, all four groups) (B); HSV infection ($p<0.001$, all four groups) (C); VZV infection ($p<0.53$, all four groups) (D). CMV, cytomegalovirus; HSV, herpes-simplex virus; VZV, varicella-zoster virus.

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Table 1. Baseline characteristics and outcomes of patients included in the analysis according to whether they developed HSV, VZV, or both infections

Characteristics	No HSV/VZV infection n=2442 (88%)	HSV infection n=229 (8.2%)	VZV infection n=92 (3.3%)	HSV and VZV infection n=18 (0.6%)
Follow-up, years, median (IQR)	3.2 (1.6, 5.1)	4.2 (2.2, 5.8)	5 (3.1, 6.1)	4.6 (3.2, 5.8)
Sex, male, n (%)	1571 (64)	129 (56)	62 (67)	8 (44)
Age at transplant, years, median (IQR)	54 (42-62)	55 (43-61)	55 (40-62)	53 (40-64)
Transplant, n (%)				
Kidney	1352 (55)	131 (57)	56 (61)	13 (72)
Liver	491 (20)	51 (22)	15 (16)	2 (11)
Lung	270 (11)	8 (3.5)	4 (4.3)	0
Heart	166 (6.8)	19 (8.3)	14 (15)	3 (17)
Others	163 (6.7)	20 (8.7)	3 (3.3)	0
Induction, n (%)	2130 (87)	194 (85)	81 (88)	15 (83)
Basiliximab	1599 (75)	154 (79)	62 (77)	12 (80)
Rabbit-antithymocyte globulins	596 (28)	41 (21)	20 (25)	3 (20)
Others	183 (8.6)	18 (9.3)	5 (6.1)	1 (6.7)
Maintenance immunosuppression, n (%)	1723 (71)	150 (66)	62 (67)	10 (59)
Tacrolimus	622 (26)	70 (31)	26 (28)	7 (41)
Cyclosporine	2207 (91)	210 (93)	85 (92)	17 (100)
MMF/MPA	99 (4.1)	8 (3.5)	7 (7.6)	1 (5.9)
m-TOR inhibitors	2252 (93)	214 (94)	92 (100)	17 (100)
Steroids	56 (2.3)	3 (1.3)	2 (2.2)	0
Other				
HSV serology, n (%)				
Positive	1418 (58)	157 (69)	56 (61)	12 (67)
Negative	486 (20)	9 (3.9)	15 (16)	2 (7.4)
Missing	538 (22)	63 (28)	21 (23)	4 (22)
VZV serology, n (%)				
Positive	2074 (85)	185 (81)	83 (90)	16 (89)
Negative	108 (4.4)	9 (3.9)	1 (1.1)	1 (5.5)
Missing	260 (11)	35 (15)	8 (8.7)	1 (5.5)
CMV serostatus, n (%)				
D+/R-	509 (21)	23 (10)	16 (17)	2 (11)
D+/R+	812 (33)	111 (49)	33 (36)	7 (39)
D-/R+	619 (25)	53 (23)	28 (30)	5 (28)
D-/R-	502 (21)	42 (18)	15 (16)	4 (22)
CMV prevention in D+/R- or R+ patients , n (%)	1007 (52)	41 (22)	36 (47)	1 (7.1)
Prophylaxis	933 (48)	146 (78)	41 (53)	13 (86)
Preemptive (including anti-herpes prophylaxis)				
Antiviral prophylaxis in D-/R- patients, n (%)	151 (30)	5 (12)	3 (20)	1 (25)
Prophylaxis	351 (70)	37 (88)	12 (80)	3 (75)
No prophylaxis				

Type of antiviral prophylaxis, n (%) (n=1264) Ganciclovir Valganciclovir Acyclovir Valacyclovir	1171 172 (15) 1003 (86) 4 (0.34) 122 (9)	51 3 (5.8) 41 (80) 0 (0) 8 (14)	40 2 (5) 35 (87) 0 (0) 4 (10)	2 0 (0) 2 (100) 0 (0) 0 (0)
Duration of antiviral prophylaxis, days, mean (SD)	147 (202)	99 (57)	122 (80)	63 (47)
Duration of antiviral prophylaxis, n (%) < 3 months of prophylaxis 3-6 months of prophylaxis > 6 months of prophylaxis	 431 (18) 560 (23) 180 (7.4)	 31 (13.5) 16 (7) 4 (1.7)	 18 (20) 18 (20) 4 (4.3)	 1 (5.6) 1 (5.6) 0 (0)
CMV infection, n (%) CMV infection previous to HSV/VZV infection, n (%)	778 (32) -	108 (47) 57 (53)	47 (51) 30 (64)	8 (44) 2 (25)
CMV disease, n (%) CMV infection previous to HSV/VZV infection, n (%)	164 (6.7) -	30 (13) 14 (47)	8 (8.7) 4 (50)	2 (11) 0 (0)
Acute rejection, n (%)	788 (32)	90 (40)	45 (49)	9 (50)
Graft loss, n (%)	166 (6.8)	22 (9.6)	7 (7.6)	1 (5.6)
Death, n (%)	301 (12)	29 (13)	6 (6.5)	1 (5.6)

CMV, cytomegalovirus; D, donor; R, recipient; IQR, interquartile range; MMF, mycophenolate mofetil; MPA, mycophenolic acid; m-TOR, mammalian target of rapamycin.

Table 2. Clinical manifestation and management of HSV and VZV infections

	HSV infection	VZV infection
Number of patients (% of all)	247 (8.9%)	110 (4.0%)
Number of infections	289	121
Time of onset from transplantation, days, median (IQR)	66 (21-336)	249 (65-738)
Seropositivity at the time of transplant	169/180 (94%)	99/101 (98%)
Mucocutaneous disease, n (%)	249 (86%)	115 (95%)
Non-mucocutaneous disease, n (%)	40 (14%)	6 (5%)
Gastrointestinal	16 (40%)	0 (0%)
Ocular	12 (30%)	2 (33%)
Viremia	5 (13%)	1 (17%)
Central nervous system	1 (2.5%)	3 (50%)
Respiratory tract	6 (15%)	0 (0%)
Antiviral therapy, n (%)	265 (93%)	119 (98%)
Reduction of immunosupression, n (%)	6/143 (4.2%)	3/66 (4.5%)
Hospitalization due to HSV or VZV infection, n (%)	12/143 (8.3%)	11/66 (17%)

Table 3. Risk factors associated with HSV infection after transplantation

	Univariate analysis			Multivariate analysis		
Variable	HR	(95% CI)	*P*	HR	(95% CI)	*P*
Age	1.006	(0.997-1.014)	0.188	0.999	(0.989-1.01)	0.906
Gender						
Male	reference					
Female	1.434	(1.114-1.845)	0.005	1.663	(1.229-2.25)	0.001
HSV serostatus						
Negative	reference					
Positive	5.082	(2.761- 9.354)	<0.001	5.198	(2.787-9.693)	<0.001
Organ Transplant						
Kidney	reference					
Heart	1.422	(0.907-2.228)	0.125	1.342	(0.817-2.205)	0.245
Liver	1.09	(0.793-1.497)	0.597	0.801	(0.553-1.161)	0.242
Lung	0.321	(0.157-0.654)	0.002	0.651	(0.301-1.408)	0.275
Other	1.222	(0.765-1.951)	0.402	1.284	(0.771-2.14)	0.336
CMV preventive strategy						
D-/R- with antiviral prophylaxis	reference					
D-/R- without antiviral prophylaxis	2.758	(1.17-6.506)	0.02	2.227	(0.894-5.549)	0.086
D+/R- or R+ anti-CMV prophylaxis	1.212	(0.519-2.828)	0.657	0.63	(0.259-1.533)	0.309
D+/R- or R+ preemptive approach	3.827	(1.691-8.661)	0.001	2.841	(1.206-6.689)	0.017

Previous CMV infection						
No	reference			reference		
Yes	2.567	(1.544-4.269)	<0.001	1.534	(0.808 – 2.91)	0.19
Induction therapy						
No	reference					
Yes	0.803	(0.568-1.136)	0.215			
Maintenance immunosuppression						
Tacrolimus	0.794	(0.61-1.035)	0.089			
MMF	0.962	(0.726-1.274)	0.785			
mTOR inhibitors	1.246	(0.723-2.144)	0.428			
Previous episode of acute rejection						
No	reference					
Yes	1.904	(1.278-2.839)	0.002	1.95	(1.235-3.077)	0.004

Table 4. Risk factors associated with VZV infection after transplantation

	Univariate analysis			Multivariate analysis		
Variable	HR	(95% CI)	*P*	HR	(95% CI)	*P*
Age	1.003	(0.991-1.016)	0.604	1.004	(0.99-1.018)	0.602
Gender						
Male	reference					
Female	0.88	(0.576-1.344)	0.555	0.958	(0.609-1.506)	0.853
VZV serostatus						
Negative	reference					
Positive	4.75	(0.663-34.153)	0.121	4.103	(0.567-29.696)	0.162
Organ Transplant						
Kidney	reference					
Heart	2.25	(1.257-4.028)	0.006	1.783	(0.942-3.376)	0.076
Liver	0.814	(0.469-1.414)	0.466	0.713	(0.388-1.309)	0.275
Lung	0.39	(0.142-1.073)	0.068	0.428	(0.151-1.218)	0.112
Other	0.436	(0.137-1.39)	0.16	0.444	(0.139-1.422)	0.172
CMV preventive strategy						
D-/R- with antiviral prophylaxis	reference					
D-/R- without antiviral prophylaxis	1.816	(0.517-6.372)	0.352	1.701	(0.477-6.068)	0.413
D+/R- or R+ anti-CMV prophylaxis	1.886	(0.582-6.108)	0.29	1.479	(0.452-4.844)	0.518
D+/R- or R+ preemptive approach	2.313	(0.718-7.457)	0.16	1.874	(0.565-6.221)	0.305

Previous CMV infection						
No	Reference			reference		
Yes	1.173	(0.365 - 3.771)	0.789	1.082	(0.331-3.539)	0.896
Induction therapy						
No	reference					
Yes	1.063	(0.581-1.946)	0.843			
Maintenance immunosuppression						
Tacrolimus	0.794	(0.521-1.208)	0.281			
MMF	1.292	(0.813-2.055)	0.278			
mTOR inhibitors	1.561	(0.756-3.226)	0.229			
Previous episode of acute rejection						
No	reference					
Yes	2.423	(1.239-4.74)	0.01	1.927	(0.93-3.991)	0.078

Table 5. Logistic regression model of the probability of HSV and VZV according to the duration of antiviral prophylaxis

	HSV infection			VZV infection		
Duration of antiviral prophylaxis	Odds ratio	95% CI	p-value	Odds ratio	95% CI	p-value
< 3months vs. no prophylaxis	0.507	(0.345 - 0.744)	0.001	0.987	(0.575 - 1.693)	0.961
3-6 months vs. no prophylaxis	0.193	(0.115 - 0.324)	<0.001	0.803	(0.469 - 1.376)	0.424
> 6 months vs. no prophylaxis	0.154	(0.056 - 0.419)	<0.001	0.567	(0.203 - 1.581)	0.278
3-6 months vs. < 3 months	0.381	(0.207 - 0.7)	0.002	0.814	(0.419 - 1.582)	0.544
> 6 months vs. < 3 months	0.303	(0.106 - 0.869)	0.026	0.575	(0.192 - 1.721)	0.322
> 6 months vs. 3-6 months	0.797	(0.263 - 2.414)	0.688	0.706	(0.236 - 2.113)	0.534